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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,697	WANG ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *5,6,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election of Group I, claims 1-4 and 7-10 in the reply filed on 6/16/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants'' election of the species Plasmodium falciparum is likewise acknowledged.

Applicants submit that the election of the above-mentioned representative species does not place an undue burden on the Examiner to perform a complete search of the defined areas. The present species elections are made without traverse to the extent that it is understood that, upon the finding of an allowable species, examination will continue until all species have been examined, or a non-allowable species is found, all in accordance with the procedures set forth in the Manual of Patent Examining Procedure § 803.02.

The inadvertent omission of claim 12 in the restriction requirement made on May 15, 2008 is regretted. As applicants correctly pointed out, claim 12 was presented in the preliminary amendments of June 13, 2008. However, since claim 12 is a

product claim hence it is withdrawn from consideration as not being distinct from the elected method claims.

Claims 5-6 and 11-12 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 16, 2008.

Status of Claims

Claims 1-12 are pending in the application.

Claims 5-6 and 11-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions.

Claim 1-4 and 7-10 are under consideration.

Specification

The disclosure is objected to because of the following informalities: there are no sequence identifier numbers for all the sequences in the specification, e.g., at page 29, Table 1.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 7 lacks antecedent basis of support or is being inconsistent with the disclosed method at e.g., page 5 of the instant specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to provide an adequate written description of the claimed method utilizing gene vaccine components of such scope particularly a library of random gene

sequences. The specification describes a method of making a polyepitopic obtained from the single organism, Malaria falciparum. Other than this single embodied organism, no other organism has been shown to produce polyepitopic chimeric gene vaccines. The disclosure does not indicate that the single embodied organism can be applied to any type of organism. Neither does the disclosure disclose which nor how the different epitopes in the numerous epitopes of an organism can be derived to produce the polyepitopic chimeric gene vaccines. In vaccine formation there is the issue of where the combination of more epitopes create many possibilities thus, making it impractical to assemble or construct library as used as a vaccine. It is impractical to assemble and construct polyepitopic gene vaccines let alone a library because it is complicated, costly and requires much work. More importantly, how to effectively design polyepitope genes and overcome the variability of pathogens is required for the development of gene vaccines. (See for example, Li M. et al. Chin. Med. J. Engl.), 112 (8), 691-7, particularly the paragraph bridging pages 691-670.) The life cycle of Plasmodium falciparum which causes malignant malaria severely affecting human health is complicated and comprises four stages comprising asexual reproduction and sexual reproduction in humans and sexual reproduction and sporogony in mosquitoes. In

humans there are exoerythrocytic (liver) and erythrocytic stages, while gametocyte and sporozoite stages are in mosquitoes. Such complex biological traits cause Plasmodium falciparum to have highly variable response against the immunoprotection of the host and drugs. It is not apparent how the different length ranges for the numerous different organisms can be ascertain based only on the single species, Malaria, given that the same organism in different species e.g., humans are different. Furthermore, it is well-known in the art that underrepresentation or overrepresentation of these different size range may not produce the e.g., epitope essential for vaccine formation.

[It is suggested that applicants recite that the polyepitopic chimeric gene is obtained from Malaria falciparum].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Non-sequitur for "the corresponding length ranges" in claim 1 step (d). Furthermore it is not clear as to the manner by which the library is in said corresponding length ranges.

2. Non-sequitur for the high diversity in step e, claim 1; "the immunogenicity" in step (f), claim 1.

3. The term "high" immunogenecity in claim 1 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to what would be considered a high immunogenic member of a gene library. This rejection has similar import to claim 7, "high" diversity. Furthermore, it is not clear as to the steps included or precluded by the scope of immunochemistry methods.

4. Claim 1 step (e) is unclear as to the detection method and the difference, if any, from step (d) diversity created by difference in length.

5. Claim 1, step (g) is unclear especially in the absence of positive support or showing in the disclosure as to how this step is accomplished.

6. Claim 7 is indefinite as to step (d) presence of a square. Should this be punctuation mark (comma)? Correction and/or clarification are required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (Chinese J of Biochemistry and (Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao) (1999), 15(6), 974-977).

Lin et al discloses throughout the article at e.g., the abstract:

> With the isocaudamers which have different recognition sequences and produce compatible cohesive ends, chimeric multi-epitope Plasmodium falciparum DNA vaccines including the multiplication of the single copy epitope and the tandem linkage of different kinds of epitopes were flexibly constructed. A specific B-cell response was detected by ELISA after the immunization of BALB/c mice with the chimeric antigen and demonstrated the usefulness of this strategy of constructing multi-epitope DNA vaccines.

Accordingly, the specific method steps of Lin using specific components fully meet the claimed method using broad components in the method.

[Applicants are required by 37 CFR 1.56 to submit information that may be material to patentability of the instant application since the above reference seems to be co-authored by one of the inventors.] See MPEP 704.12(a)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sette et al (USP 7026443) or Fikes (USP 6602510) in view Richards et al (USP 6291214) or applicants' admission of known prior art.

Sette et al discloses throughout the patent at e.g., col. 5, line 65 up to col.6, line 11:

> ...Methods for monitoring or evaluating an immune response to HPV in a patient having a known HLA-type. Such **methods** comprise incubating a T lymphocyte sample from the patient with a peptide composition comprising an HPV epitope that

has an amino acid sequence described in Tables VII to Table XX which binds the product of at least one HLA allele present in the patient, and detecting for the presence of a T lymphocyte that binds to the peptide. A CTL peptide epitope may, for example, be used as a component of a tetrameric complex for this type of analysis……
An alternative modality for defining the peptide epitopes is to recite the physical properties, such as length……

Sette et al further discloses at e.g., col. 10, lines 10-22:

A **"vaccine"** is a composition that contains one or more peptides of the invention. There are numerous embodiments of **vaccines** in accordance with the invention, such as by a cocktail of one or more peptides; one or more epitopes of the invention comprised by a **polyepitopic** peptide; or nucleic acids that encode such peptides or polypeptides, e.g., a minigene that encodes a **polyepitopic** peptide. The "one or more peptides" can include any whole unit integer from 1-150, e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 or more peptides of the invention.

Sette discloses in e.g., Example 10

This example illustrates the procedure for the selection of peptide epitopes for **vaccine** compositions of the invention. The peptides in the composition can be in the form of a nucleic acid sequence, either single or one or more sequences (i.e., minigene) that encodes peptide(s), or can be single and/or **polyepitopic** peptides.

The following principles are utilized when selecting an array of epitopes for inclusion in a **vaccine** composition. Each of the following principles is balanced in order to make the selection.

When creating a **polyepitopic** compositions, e.g. a minigene, it is typically desirable to generate the smallest peptide

possible that encompasses the epitopes of interest. The principles employed are similar, if not the same, as those employed when selecting a peptide comprising nested epitopes.

In cases where the sequences of multiple variants of the same target protein are available, potential peptide epitopes can also be selected on the basis of their conservancy. For example, a criterion for conservancy may define that the entire sequence of an HLA class I binding peptide or the entire 9-mer core of a class II binding peptide be conserved in a designated percentage of the sequences evaluated for a specific protein antigen. (Reads on claim 1, step d)

In Example 11 Sette discloses:

Construction of Minigene Multi-epitope DNA Plasmids

This example provides general guidance for the construction of a minigene expression plasmid. Minigene plasmids may, of course, contain various configurations of CTL and/or HTL epitopes or epitope analogs as described herein. Examples of the construction and evaluation of expression plasmids are described, for example, in co-pending U.S. Ser. No. 09/311,784.

A minigene expression plasmid typically includes multiple CTL and HTL peptide epitopes. In the present example, HLA-A2, -A3, -B7 supermotif-bearing peptide epitopes and HLA-A1 and -A24 motif-bearing peptide epitopes are used in conjunction with DR supermotif-bearing epitopes and/or DR3 epitopes. HLA class I supermotif or motif-bearing peptide epitopes derived from multiple HPV antigens, preferably including both early and late phase antigens, are selected such that multiple supermotifs/motifs are represented to ensure broad population coverage. Similarly, HLA class II epitopes are selected from multiple HPV antigens to provide broad population coverage, i.e. both HLA DR-1-4-7 supermotif-bearing epitopes and HLA DR-3 motif-bearing epitopes are selected for inclusion in the minigene construct. The selected CTL and HTL epitopes are then

incorporated into a minigene for expression in an expression vector.

This example illustrates the **methods** to be used for construction of a minigene-bearing expression plasmid. Other expression vectors that may be used for minigene compositions are available and known to those of skill in the art.

Overlapping oligonucleotides that can, for example, average about 70 nucleotides in length with 15 nucleotide overlaps, are synthesized and HPLC-purified. The oligonucleotides encode the selected peptide epitopes as well as appropriate linker nucleotides, Kozak sequence, and signal sequence. The final multiepitope minigene is assembled by extending the overlapping oligonucleotides in three sets of reactions using PCR…….

For example, a minigene can be prepared as follows. For a first PCR reaction, each of two oligonucleotides are annealed and extended: In an example using eight oligonucleotides, i.e., four pairs of primers, oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined…. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended for 10 cycles. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product. The full-length product is gel-purified and cloned into pCR-blunt and individual clones are screened by sequencing.

Fikes at e.g., throughout the patent at e.g., col. 30, line 35:

IV.J.1. **Minigene** Vaccines

A number of different approaches are available which allow simultaneous delivery of multiple epitopes. Nucleic acids encoding multiple epitopes are a useful embodiment of the invention; discrete peptide epitopes or **polyepitopic**

peptides can be encoded. The epitopes to be included in a **minigene** are preferably selected according to the guidelines set forth in the previous section. Examples of amino acid sequences that can be included in a **minigene** include: HLA class I epitopes, HLA class II epitopes, a ubiquitination signal sequence, and/or a targeting sequence such as an endoplasmic reticulum (ER) signal sequence to facilitate movement of the resulting peptide into the endoplasmic reticulum.

…..A multi-epitope DNA plasmid encoding nine dominant HLA-A*0201- and A11-restricted CTL epitopes derived from the polymerase, envelope, and core proteins of HBV and human immunodeficiency virus (HIV), a PADRE.RTM. universal helper T cell (HTL) epitope and an endoplasmic reticulum-translocating signal sequence have been engineered. Immunization of HLA transgenic mice with this plasmid construct resulted in strong CTL induction responses against the nine CTL epitopes tested.

For example, to create a DNA sequence encoding the selected epitopes (**minigene**) for expression in human cells, the amino acid sequences of the epitopes may be reverse translated. A human codon usage table can be used to guide the codon choice for each amino acid. These epitope-encoding DNA sequences may be directly adjoined, so that when translated, a continuous polypeptide sequence is created. However, to optimize expression and/or immunogenicity, additional elements can be incorporated into the **minigene** design such as spacer amino acid residues between epitopes.

The **minigene** sequence may be converted to DNA by assembling oligonucleotides that encode the plus and minus strands of the **minigene**. Overlapping oligonucleotides (**30-100 bases long**) may be synthesized, phosphorylated, purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. This synthetic **minigene**, encoding the epitope polypeptide, can then be cloned into a desired expression vector……

……Optimized peptide expression and immunogenicity can be achieved by certain modifications to a **minigene** construct……

Once an expression vector is selected, the **minigene** is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate bacterial strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the **minigene,** as well as all other elements included in the vector, are confirmed using restriction mapping and DNA sequence analysis. Bacterial cells harboring the correct plasmid can be stored as cell banks.

Target cell sensitization can be used as a functional assay of the expression and HLA class I presentation of **minigene**-encoded epitopes. For example, the plasmid DNA is introduced into a mammalian cell line that is a suitable target for standard CTL chromium release assays. The transfection method used will be dependent on the final formulation, electroporation can be used for "naked" DNA, whereas cationic lipids allow direct in vitro transfection. A plasmid expressing green fluorescent protein (GFP) can be co-transfected to allow enrichment of transfected cells using fluorescence activated cell sorting (FACS). The transfected cells are then chromium-51 (.sup.51 Cr) labeled and used as targets for epitope-specific CTLs. Cytolysis of the target cells, detected by .sup.51 Cr release, indicates both the production and HLA presentation of, **minigene**-encoded CTL epitopes. Expression of HTL epitopes may be evaluated in an analogous manner using assays to assess HTL activity.

In vivo immunogenicity is a second approach for functional testing of **minigene** DNA formulations. Transgenic mice expressing appropriate human HLA proteins are immunized with the DNA product…..Once again, lysis of target cells that were exposed to epitopes corresponding to those in the minigene, demonstrates DNA vaccine function and induction of CTLs. Immunogenicity of HTL epitopes is evaluated in transgenic mice in an analogous manner.

Richards discloses throughout the patent at e.g., col. 25, lines 7-25:

Both within and external to the lacZ.alpha. gene we have incorporated restriction enzyme sites needed for compatibility with commercial cDNA library synthesis methods. These include methods for either partial or random fragments. Most of these will not have the translation-initiation sites needed for protein expression. Therefore, it is desirable to have an efficient translation start site available on the cloning vector…….The restriction enzyme Esp3AI is an isocaudamer of EcoRI and so the pSK213 vector is compatible with EcoRI/XhoI-derived methods. This allows one to create one cDNA and clone it into the vector twice; once at the EcoRI site and including prokaryotic transcription, and a second time at the Esp3AI site and exclude transcription from occurring in E. coli.

Applicants at page 10, line 5-6 disclose:

….Various 5 isocaudamers are known in the art, which may be used in the method of the present invention.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use isocaudamer linkage in the method of either Sette or Fikes for the advantage taught by Richards above. Because of this known advantage one would be motivated to use said linkage. One would have a reasonable expectation of success in obtaining a polyepitopic chimera gene vaccine since as applicants acknowledge said various linkage had been used and are known in the art in making polyepitopic chimeric gene vaccine.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639